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Evaluation of Neutrophil/Lymphocyte Ratio Changes Between Pre- and Post-menopausal Life for Cardiovascular Risk Prediction

Kardiyovasküler Risk Tahmini İçin Pre- ve Post-menopozal Hayatta Nötrofil/Lenfosit Oranı Değişikliklerinin Değerlendirilmesi

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ABSTRACT

AIM: *Neutrophil to lymphocyte ratio (NLR) has demonstrated in various clinical studies to identify the increased atherosclerotic cardiovascular risk. However, the prognostic value of NLR is unknown in healthy postmenopausal women. The aim of this study to evaluate the relationship between and premenopausal and postmenopausal healthy women regarding the NLR.*

METHODS: *The study population included 295 premenopausal (median age 37 years, range 33–42 years) and 153 postmenopausal (median age 56 years, range 52–62 years) healthy women who have admitted cardiology clinic between March 2013 and May 2014. The complete blood count was obtained from all patients. Total leukocytes were counted and differential count obtained for neutrophil, lymphocyte and NLR were evaluated.*

RESULTS: *There were no significant differences between premenopausal and postmenopausal healthy women regarding NLR (median: 1.77 [interquartil range (IQR): 1.38–2.25], and 1.68 [IQR: 1.24–2.07], p=0.240 respectively). Similarly, there were no significant differences between two groups in terms of neutrophil and lymphocyte counts (median: 3.7×103/mm³ [IQR: 3.04–4.50] vs. 3.63×103/mm³ [IQR: 2.79–4.33], p=0.393 and 2.12 [IQR: 1.79–2.52] vs. 2.10 [IQR: 1.70–2.60], p=0.624, respectively).*

CONCLUSION: *This study demonstrated that there is no difference regarding NLR between the premenopausal and healthy postmenopausal women. These findings have also revealed that the NLR, neutrophil and lymphocyte counts do not change in menopausal life, and thus can not be used as a marker for atherosclerosis in these groups.*

Key words: *neutrophil/lymphocyte ratio; neutrophil; lymphocyte; menopause; cardiovascular risk*

ÖZET

AMAÇ: *Birçok klinik çalışmada nötrofil lenfosit oranının (NLO), artmış aterosiklerotik kardiyovasküler risk belirlemede prognostik değerinin bilinmesine rağmen, postmenopozal sağlıklı kadınlarda ki prognostik değeri bilinmemektedir. Bu çalışmanın amacı, premenopozal ve postmenopozal sağlıklı kadınlar arasında NLO değerlendirmektir.*

YÖNTEM: *Mart 2013 ve Mayıs 2014 tarihleri arasında kardiyoloji polikliniğine kontrol maksatlı başvuran ve herhangi bir kardiyak yakınması olmayan premenopozal 295 (ortanca yaş 37 yıl, dağılım 33–42 yıl) ve postmenopozal 153 kadın (ortanca yaş 56 yıl, dağılım 52–62 yıl) çalışmaya alındı. Tüm hastaların tam kan hücre sayıları kaydedildi. İki grup arasında rutin kan sayım parametreleri nötrofil, lenfosit ve nötrofil lenfost oranı (mutlak nötrofil sayısının ve mutlak lenfosit sayısına oranı) karşılaştırıldı.*

BULGULAR: *Premenopozal ve postmenopozal sağlıklı kadınlar arasında nötrofil-lenfosit oranı açısından istatistiksel fark saptanmadı (sırasıyla median: 1,77 [interquartil range (IQR): 1,38–2,25] ve 1,68 [IQR: 1,24–2,07], p=0,240). Benzer şekilde, lokosit ve lenfosit sayıları arasında da istatistiksel fark saptanmadı (sırasıyla, median: 3,7×103/mm³ [IQR: 3,04–4,50] kr. 3,63×103/mm³ [IQR: 2,79-4,33], p=0,393 ve 2,12 [IQR: 1,79-2,52] kr. 2,10 [IQR: 1,70–2,60], p=0,624).*

SONUÇ: *Bu çalışma, NLO'yu postmenopozal dönem ile premenopozal dönem arasında fark olmadığı göstermiştir. Ayrıca bu sonuçlar, nörofil, lenfosit sayılarının ve NLO'nun postmenopozal dönemde farklılık göstermediğini ve ateroskleroz riski belirteci olarak kullanılılamaz olduğunu ortaya koymuştur.*

Anahtar kelimeler: *nörofil/lenfosit oranı; nötrofil; lenfosit; menopoz; kardiyovasküler risk*

Introduction

The menopause is the permanent discontinuance of menstruation due to the loss of ovarian follicular activity. Clinically, menopause is diagnosed after twelve months of amenorrhea, so the time of the final menses is determined retrospectively[1]. Loss of ovarian follicular

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function results in decreased circulating estrogen levels. Several studies have shown protective effects of estrogen against atherosclerosis[2]. The incidence of cardiovascular events gradually increases in postmenopausal women, which may be due to increases in risk factors and diminished levels of estrogen[3,4]. Atherosclerotic cardiovascular disease is responsible for approximately one-third of deaths worldwide[5]. Atherosclerosis is a particular form of the systemic chronic low-grade inflammatory process resulting from interactions between humoral, cellular mediators and multiple risk factors[6]. The important role of neutrophils, lymphocytes, monocytes in atherosclerosis has been well established[7–11]. The NLR is used as indicators of systemic inflammation in various conditions. Also, it was suggested that NLR has prognostic value in some atherosclerotic diseases[12,13].

It is well-known that menopause has unfavorable effects on lipid profile, but its impact on neutrophil, lymphocyte count, and NLR is unknown[2,4,14]. The goal of this study was to determine if there were differences in inflammatory parameters of complete blood count (CBC) regarding the neutrophil, lymphocyte count, and NLR between premenopausal and postmenopausal women and to evaluate whether the NLR could be a predictor of chronic inflammation.

Methods

This retrospective study included 448 healthy women (n=448) who were admitted to our cardiology clinic between March 2013 and May 2014. These 448 women were divided into two groups, a premenopausal group (n=295) and the postmenopausal group (n=153). All patients were provided informed consent, and the study was approved by the local ethic committee.

Exclusion criteria included the presence of the irregular menstrual cycles, history of hormone replacement therapy (HRT), infection in the last one month, high body temperature (>38 °C), and the history of an inflammatory disease. The patients with a known coronary artery disease, valvular heart disease, history of rhythm disturbances, abnormal electrocardiography (ECG), left ventricular systolic dysfunction, cerebral or peripheral vascular disease, hematological disorders, renal or liver insufficiency, and thyroid dysfunction have also excluded the study.

All subjects were evaluated with physical examination, CBC, routine biochemical examination, ECG and echocardiography (ECHO). Venous blood samples were taken from patients after a 12-hour fasting and analyzed for CBC parameters. The CBC parameters including the white blood count (WBC), hemoglobin (Hb), platelet, mean platelet volume (MPV), neutrophil, and lymphocyte were tested. Also, the biochemical parameters including the total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and glucose levels were tested. NLR was calculated as the ratio of neutrophil cell count to lymphocyte cell count using COBAS c311 analyzer system (Roche Diagnostics, Germany).

Statistical Analysis

The Statistical Package for the Social Sciences software (SPSS 20.0 for Windows, Inc., Chicago, IL, USA) was used for all statistical calculations. The Kolmogorov-Smirnov test was used to determine the distribution of data from continuous variables. Normally distributed data were given as mean±standard deviation (SD), data with non-normal distributions were expressed as median, and the interquartil ratio (IQR), and dichotomous data were given as a percent. A significance level of the difference between the premenopausal and postmenopausal group was analyzed using Student-t test for parametric value and Mann-Whitney U test for not normal distributing variables. Differences between dichotomous variables were evaluated using the χ^2 test. Correlations between NLR and various parameters were assessed using Spearman correlation test. Statistical significance was defined as $p<0.05$.

Results

The median age of the all study population was 42 years (IQR: 35.25–53 years). The median age and body mass index (BMI) of premenopausal (37 [IQR 33–42] years, and 25.91 [IQR 22.89–30.83] kg/m^2) and postmenopausal (56 [IQR 62–62] years, and 28.47 [IQR 25.87–31.21] kg/m^2) women were recorded respectively. Compared with premenopausal women, weight, BMI, Hb, Hct and fasting blood glucose levels were significantly higher in postmenopausal women, whereas mean height and smoking ratio were comparable between two groups. There were no significant differences between two groups with respect to MCV and RDW values. Postmenopausal women showed statistically significant increase in serum TC, TG, LDL-C levels. TC/HDL-C, LDL-C/HDL-C,

and TG/HDL-C ratio were significantly increased in postmenopausal women as compared to that in premenopausal women. In contrast, HDL-C levels did not show a statistically significant difference between two groups. Clinical and laboratory features of two groups are given in Table 1.

Our study has primarily focused on the effects of menopause on neutrophil, lymphocyte count and NLR in healthy women who do not receive an HRT. The median of NLR were 1.77 (IQR 1.38–2.25) in premenopausal and 1.68 (IQR 1.24–2.07) in postmenopausal women respectively. This difference was not statistically significant (p=0.24). Similarly there were no significant differences between the two groups in terms of neutrophil (median [IQR] 3.7×10^3/mm^3 [30.04–4.50] vs. 3.63×10^3/mm^3 [2.79–4.33], p=0.7393) and lymphocyte counts (2.12 [1.79–2.52] vs. 2.10 [1.70–2.60], p=0.624, respectively). WBC, MPV median values, and platelet count were found to be similar between two groups. Hematological parameters and NLR values are given in Table 2.

There were negative correlations between NLR and FBG, Hb, MCHC, RDW, TC, LDL-C, TG, LDL-C/HDL-C and TC/HDL-C levels. Parameters correlated with NLR are given in Table 3.

Discussion

Menopause is defined as the permanent discontinuation of menstruation resulting from loss of ovarian follicular activity and l2 months of amenorrhea from the last menstrual period. The final menstrual period (FMP) usually occurs between the ages of 40 and 58. The average age of menopause is 51 years[15,16]. World Health Organization (WHO) has recommended the use of the following definitions for menopause status categories. Premenopausal period is defined as the entire reproductive period before FMP and the postmenopausal period is defined as dating from the FMP[1]. Stages of reproductive Aging (STRAW) Workshop group divided the adult female life into three broad phases as the reproductive, menopausal transition, and postmenopause. These three phases consist of seven

Table 1. *Demographic characteristics and laboratory parameters of two groups*

Parameters	Premenopausal group (n=295)	Postmenopausal group (n=153)	p value
Age (years)	37 (33–42)	56 (52–62)	<0.001
Weight (kg)	68 (59–82)	74 (67–80)	<0.001
Height (cm)	163 (158.75–166)	162 (15875–165)	0.136
BMI (kg/m^2)	25.91 (22.89–30.83)	28,47 (25.87–31.21)	<0.001
Smoking, n (%)	76 (25.76)	41 (26.79)	0.813
Hb (g/dL)	12.40±1.47	13.09±1.30	<0.001
HTC (%)	37.08±3.34	38.85±3.31	<0.001
MCV(fL)	83.6 (79.70–87)	84.05 (80.87–86.90)	0.564
MCHC (gHb/dL)	33.29±2.63	31.29±8.87	<0.05
RDW (%)	14.02±2.08	13.80±1.78	0.261
FBG (mg/dL)	98 (92–104)	102 (98–107.25)	<0.001
TC (mg/dL)	190 (165–212)	224 (197–251.25)	<0.001
TG (mg/dL)	88 (62–126)	129 (96.75–184.75)	<0.001
HDL-C (mg/dL)	55 (46–66)	53 (42–60.25)	0.069
LDL-C (mg/dL)	111 (87–129)	139 (117.75–159.75)	<0.001
TC/HDL-C	3.41 (2.69–4.21)	4.35 (3.61–5.30)	<0.001
LDL-C/HDL-C	2 (1.44–2.58)	2.78 (2.16–3.37)	<0.001
TG/HDL-C	1.66 (0.96–2.60)	2.47 (1.68–4.27)	<0.001

BMI, body mass index; Hb, hemoglobin; HTC, hematocrit; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; RDW, erythrocyte distribution width; FBG, fasting blood glucose; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.
Data is expressed as number and % of patients, mean±SD or median (interquartil range [IQR] 25th–75th).

Table 2. *Neutrophil-to-lymphocyte ratio and other circulatory blood cell count of two groups*

Parameters	Premenopausal (n=295)	Postmenopausal (n=153)	p
WBC (10^3/mm^3)	6.58 (5.63–7.84)	6.23 (5.47–7.51)	0.075
Nc (10^3/mm^3)	3.70 (3.04–4.50)	3.63 (2.79–4.33)	0.393
Lc (10^3/mm^3)	2.12 (1.79–2.52)	2.10 (1.70–2.60)	0.624
NLR	1.77 (1.38–2.25)	1.68 (1.24–2.07)	0.240
Pc (10^3/mm^3)	261 (220–306.75)	257 (225.50–288)	0.508
MPV (μm^3)	10.36±1.20	10.39±0.92	0.781
RDW (%)	14.02±2.08	13.80±1.78	0.284

WBC, white blood cell count; Nc, neutrophil count; Lc, lymphocyte count; NLR, neutrophil to lymphocyte ratio; Pc, platelets count; MPV, main platelet volume; RDW, erythrocyte distribution width.
Data are expressed as mean±SD or median (interquartil range [IQR] 25th–75th).
P value is significant less than at the 0.05 level in the between groups.

Table 3. *A linear relationship between neutrophil to lymphocyte ratio and the other continuous variables*

	Premenopausal+postmenopausal groups (n=448)	
Parameters	r	p
FBG (mg/dL)	-0.114	0.016
Hb (g/dL)	-0.100	0.035
MCHC (g/dL)	-0.120	0.011
RDW (%)	-0.094	0.048
TC (mg/dL)	-0.109	0.021
LDL-C (mg/dL)	-0.093	0.049
TG (mg/dL)	-0.109	0.021
LDL-C/HDL-C	-0.105	0.026
TC/HDL-C	-0.122	0.010

FBG, fasting blood glucose; Hb, hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, erythrocyte distribution width; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol.

stages centered on the FMP (Stage 0). The reproductive phase was divided into Stages -5, -4, and -3 corresponding to early, peak, and late, respectively. The menopausal transition phase consisted of Stage -2 (early) and Stage -1 (late), and the postmenopausal phase contained Stages +1 (early) and +2 (late)[6]. The oocytes in the ovaries undergo atresia throughout a women's life cycle, and both the quantity and quality of follicles fall into a sharp decline. Estradiol (E2), the most potent form of the hormone, is predominant before menopause while estrone (E1) is the primary form of menopause. Also, levels of both hormones are considerably lower in postmenopausal period than the premenopausal period[17,18].

Studies have shown that after menopause, women demonstrate an increased risk of atherosclerotic heart disease[17,18]. It is assumed that menopause-related hormonal changes (decreased level of estrogen, especially E2) are associated with the development of the atherosclerotic cardiovascular disease. Changes in estrogen level may influence inflammatory processes during the menopausal period. It has been shown that menopause causes low grade of systemic inflammation[19]. Several studies demonstrated that chronic low grade inflammation increases the risk of cardiovascular disease[20] Besides, HRT has been shown to reduce serum markes of inflammation and the incidence of cardiovascular disease in postmenopausal women[21–23].

WBC count refers to the total number of white blood cells in the peripheral blood produced by the bone marrow. It has been related to different cardiovascular risk factors, such as smoking, obesity, and hypertension[10,24,25]. WBC and its fractions including neutrophils and lymphocytes provide an indirect estimate of inflammatory status[10,13,26].

NLR, the simple ratio obtained from a differential blood cell count, was introduced as a marker to determine inflammation in various disorders such as cardiovascular diseases, malignancies, and diabetes mellitus. It is used as a predictor of adverse cardiovascular outcomes in atherosclerotic heart disease. It was demonstrated that it has an association with the coronary artery disease, pulmonary arterial hypertension, coronary ectasia, arrhythmias, atherosclerotic coronary artery disease, as well as the severity of acute coronary syndromes and the survival after coronary artery disease[13,26–30].

Several studies have demonstrated that the parameters of blood samples including TC, LDL, and TG levels are increased after menopause[4,31]. However, the effect of menopause on neutrophil, lymphocyte count, and

NLR is unknown. We found no statistically significant differences between two groups in respect of neutrophil, lymphocyte count and NLR (p=0.393, p=0.624, and p=0.240, respectively).

This research is the first, regarding the investigation of neutrophil, lymphocyte count and NLR in premenopausal and postmenopausal healthy women. Our study has primarily focused on the effects of menopause on neutrophil, lymphocyte count and NLR in healthy women who do not receive an HRT. To the best of our knowledge, no study has investigated the NLR in healty postmenopausal women, for this reason we were unable to compare our results with other studies. Angeli et al.[32] examined 298 hypertensive postmenopausal women and showed that, in addition to traditional risk factors, neutrophil count identifies hypertensive postmenopausal women at increased risk of cardiovascular disease. In that study, total WBC count did not show any association with cardiovascular events. Another study found that NLR was significantly increased in postmenopausal osteopenic women, which may be used as the indicator of bone loss[33].

TC, LDL-C and TG levels progressively increase during menopausal period[31]. However, studies examining the influence of menopause on HDL-C have yielded conflicting results. Some concluded that the menopause is not associated with change in HDL-C, while others concluded that menopause is associated with a decline in HDL-C[34]. In our study TC, LDL-C and TG levels were significantly higher in postmenopausal women compared to that of premenopausal women. In contrast, HDL-C levels did not show a statistically significant difference between two groups.

In conclusion, NLR which is an emerging marker of inflammation, is used as a predictor of adverse outcomes in atherosclerotic heart disease. Our results suggest that menopause does not alter NLR in healthy women. For this purpose, the large-scale controlled prospective studies are needed to assess the effect of menopause on humoral and cellular inflammatory markers.

Limitation of the Study

The main limitations of this study include: single centered/relatively small number of subjects and retrospective design; did not asses the hormone levels; invasive study was not performed to exclude coronary artery disease; and humoral and cellular inflammatory markers were missing from the study data.

Conflict of Interest

The authors declare no conflict of interest.

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